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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/625,047	MEARES ET AL.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6,8,10-24,26,27,30 and 33-39* is/are pending in the application.

4a) Of the above claim(s) *16-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 6, 8, 10-15, 24, 26-27, 30 and 33-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/31/2007 has been entered.

Claims 1, 6, 8, 10-24, 26-27, 30 and 33-39 are pending

Claims 16-23 are withdrawn from consideration as being drawn to non-elected inventions.

Claims 1, 6, 8, 10-15, 24, 26-27, 30 and 33-39 are currently under consideration.

Rejections Withdrawn:

The rejection of Claims 1, 6-8, 10-15, 24, 26-27, 30 and 33-36 under 35 U.S.C. 102(b) as being anticipated by Hansen et al. (WO 99/66951) is withdrawn in view of Applicants amendments which recites that the antibody comprises a reactive site within the structure of the antibody that is not present in the wildtype of said antibody, wherein said reactive site is in a position within said antigen recognition domain.

All other rejections and/or objections are withdrawn in view of applicant's amendments and arguments there to.

New Objections and/or Rejections:

Claim Objections

Claim 39 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. In the instant case, claim 39 recites the limitation that the antibody used in the method of independent claim 1 is purified. However, it is unclear how this limitation further limits the antibody used in the method of claim 1.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6, 8 and 33-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 6 recites the limitation "said substituted or unsubstituted DOTA". However, there is insufficient antecedent basis for this limitation in the claim since independent claim 1, from which claim 6 depends, does not appear to set forth that DOTA is substituted or unsubstituted.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a subject with cancer by administration of a macrocyclic metal chelate, said method comprising the steps of: administering to said subject an antibody comprising an antigen recognition domain that recognizes said macrocyclic metal chelate, wherein said antibody comprises: a reactive site within the structure of the antibody that is not present in the wildtype of said antibody, wherein said reactive site is in a position within said antigen recognition domain and said antibody comprises a variable light chain region comprising the amino acid sequence of SEQ ID NO: 1 and variable heavy chain region comprising the amino acid sequence of SEQ ID NO: 5 or an antibody comprising CDR1, CDR2 and CDR3 of the VL chain of SEQ ID NO: 1 (SEQ ID NOs: 2, 3 and 4, respectively) and CDR1, CDR2, and CDR3 of the VH chain of SEQ ID NO: 5 (SEQ ID NOs: 6, 7 and 8 respectively), does not provide enablement for an antibody comprising a first sequence having at least 95% homology with SEQ IDNO: 1; a second sequence having at least 95% homology with SEQ ID NO: 5; wherein the antibody comprises a reactive site within the structure of the antibody that is not present in the wildtype of

said antibody. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The instant claims broadly encompass a method of using an antibody comprising a first sequence having at least 95% homology with SEQ IDNO: 1; a second sequence having at least 95 homology with SEQ ID NO: 5; wherein the antibody comprises a reactive site within the structure of the antibody that is not present in the wildtype of said antibody, wherein said reactive site is in a position within said antigen recognition domain and an antigen recognition domain that recognizes substituted or unsubstituted 1,4,7,10-tetraazacyclododecane-N,N',N",N"'-tetraacetic acid (DOTA). Thus, the claims encompass homologs of SEQ ID NO:1 and/or 5, wherein the "variation" represented by 95% homology occurs within the 3 CDR's of SEQ ID NO: 1 or the 3 CDR's of SEQ ID NO: 5.

The scope of the instant claims is not commensurate with the enablement of the instant disclosure, because practice of the claimed invention would require undue experimentation by an artisan of ordinary skill in the art. The instant specification is not enabling for claims drawn to an antibody comprising a first sequence having at least 95% homology with SEQ IDNO: 1; a second sequence having at least 95 homology with SEQ ID NO: 5, wherein the antibody comprises a

reactive site within the structure of the antibody that is not present in the wildtype of said antibody, wherein said reactive site is in a position within said antigen recognition domain and an antigen recognition domain that recognizes substituted or unsubstituted 1,4,7,10-tetraazacyclododecane-N,N',N",N"'-tetraacetic acid (DOTA). The specification teaches (paragraph 0048) that an "antigen recognition domain" refers the part of the antibody, recombinant molecule, the fusion protein, or the immunoconjugate of the invention which recognizes the target or portions thereof, wherein the antigen recognition domain comprises the variable region of the antibody or a portion thereof, e.g., one, two, three, four, five, six, or more hypervariable regions. The specification further teaches (paragraph 0108) an antibody which has been engineered to contain a cysteine residue at positions 53 of the light chain or an aspartic acid at position 87 of the heavy-chain or a cysteine at position 53 and an aspartic acid at position 87 of the heavy chain or a cysteine at position 54 and an aspartic acid at position 87 of the heavy chain or a cysteine at position 55 and an aspartic acid at position 87 of the heavy chain of a 2D12.5 antibody which binds a macrocyclic metal chelate. With regards to 2D12.5, the specification teaches (page 4, paragraph 0010) that the anti-chelate antibody, 2D12.5, possess a high binding affinity for (S) nitrobenzyl DOTA chelates and Janus DOTA chelates. For example, the specification teaches an evaluation of the crystal structure of 2D12.5 bound to its hapten, Y-DOTA, identified two specific side-arm orientations of the chelate in the binding pocket (Example 1). Thus, while the specification clearly establishes a correlation between the reactive sites location proximate to or within the antigen recognition domain of SEQ ID NO: 1 or 5 (light and heavy chains of 2D12.5 respectively) and specific antigen recognition of the macrocyclic metal chelate, DOTA, the specification appears to be silent on any homologs of the amino acid sequences of SEQ ID NO: 1 and/or 5, wherein the variation occurs within the CDR's.

In the instant case, it is well established in the art that the formation of an intact antigen-binding site of all antibodies requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs or hypervariable regions, which provide the majority of the contact residues for the binding of the antibody to its target epitope (Paul, Fundamental Immunology, (textbook), 1993, pp. 292-295), under the heading "Fv Structure and Diversity in Three Dimensions"). The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity, which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light

chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites (Paul, page 293, first column, lines 3-8 and line 31 to column 2, line 9 and lines 27-30). Even minor changes in the amino acid sequence of the heavy and light chain variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al. (Proc. Natl Acad. Sci. USA 1982; 79: 1979). Rudikoff et al. teach that an alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that an antibody as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions of an antibody, have the required binding function. The specification provides no direction or guidance regarding how to produce antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

Therefore, in view of the lack of predictability in the art as evidenced by the references cited above and in view of the lack of guidance in the specification and in view of the broadly claimed invention, one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 6, 8, 10-15, 24, 26-27, 30, 33-36 and 38-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hansen et al. (WO 99/66951, of record) in view of Chmura et al. (PNAS 2001; 98: 8480-8484).

Hansen et al. teach a method of treating diseased tissues in a patient, comprising: (a) administering to a patient a bi-specific antibody or antibody fragment having at least one arm that specifically binds to a targeted tissue and at least one arm that specifically binds a targetable conjugate; (b) optionally, administering to said patient a clearing composition, and allowing said composition to clear non-localized antibodies or antibody fragments from circulation; and (c) administering to said patient a first targetable conjugate which comprises a carrier portion which comprises or bears at least one epitope recognizable by said at least one other arm of said bi-specific antibody or antibody fragment, and one or more therapeutic agents (page 58, claim 1 of WO document). With regards to the targetable conjugate's epitope, the WO document teaches (page 9, lines 30-33) that the epitope includes, but is not limited to, a hapten. With regards to the hapten, Hansen et al. teach (page 10, line 2 and page 34, lines 27-28) that haptens include, but are not limited to, chelators such as DPTA and DOTA. For example, the WO document teaches (page 35, lines 7-11) a method of treating CEA-expresing tumors, wherein a bi-specific antibody with at least one arm, which specifically binds to CEA, and at least one arm, which specifically binds the targetable conjugate whose hapten is a conjugate of yittruim-DOTA is administered to a patient. With regards to the bi-specific antibody which recognizes CEA and a metal chelate such as DOTA, the WO document teaches (page 10, lines 26-33) that the bi-specific antibody is generated by derivatizing an anti-CEA $F(ab')_2$ mAB with a hydrazide-maleimide cross-linker and coupling said derivatized anti-CEA $F(ab')_2$ to an anti-chelate Fab'-SH. Moreover, Hansen et al. teach (page 24, lines 24-33) that chelators, such as DOTA, may be conjugated to the carrier portion of a targetable conjugate by generating a reactive functional group such as carbodiimide and coupling the carbodiimide to the peptides free amines. Thus, while Hansen et al. does not teach a macrocyclic metal chelate comprising four nitrogen atoms as shown in the formula of claim 6 or an S configuration DOTA, the referenced limitations are an inherent structural feature of DOTA as evidenced by Sigma-Aldrich (see attached document of record). Thus, the claimed antibody appears to recognize the same macrocyclic metal chelate as the prior art. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that a product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In

re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Hansen et al. does not explicitly teach that that the antibody comprises a reactive site within the structure of the antibody that is not present in the wildtype of said antibody, wherein said reactive site is in a position within said antigen recognition domain. Nor does Hansen et al. teach that the macrocyclic DOTA contain a functional group which is reactive with the reactive site of the antibody.

Chmura et al. teach a method of producing antibodies having infinite affinity with a ligand, wherein the antibodies comprise a chemically reactive site such as a cysteine near the ligand-binding site of the antibody; and the ligand comprises an electrophilic substituent designed to form a stable thioether bond on reaction with the cysteine side chain of the antibody (Title and page 8480, 2nd column, 3rd full paragraph and 4th full paragraph). While the reference teaches that the chemical manipulation of affinity is applicable to other biological binding pairs, the antibody used was the anti-chelate antibody CHA255 and the ligand used was (S)-benzyl-EDTA-indium chelates since the anti-chelate antibody possess high affinity for (S)-benzyl-EDTA-indium chelates and exquisite specificity for these small molecules (page 8480, 2nd column, 3rd full paragraph and 4th full paragraph). In particular, the reference teaches that a slow rate of dissociation is particularly important for in vivo targeting application, where a targeted therapeutic drug requires a long period on the target to be effective (page 8480, 2nd column, 1st full paragraph). However, the reference teaches that most natural antibodies, as well as engineered fragments, against small molecule possess only a single ligand binding site; and therefore, only remain bound to its ligand for an average period of a few minutes to a few hours (page 8480, 2nd column, 1st full paragraph). As such, the reference teaches that the surest way to prolong the lifetime of a complex is to make a covalent bond between its components (page 8480, 2nd column, 2nd full paragraph).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references so as to modify the anti-chelate antibody and chelate, e.g., DOTA, used in the method taught by Hansen et al. in view of the teachings of Chmura et al.. One would have been motivated to do so because Chmura et al. teach a method of generating an antibody having infinite affinity for a ligand which is applicable for to other ligand binding pairs, wherein the antibody forms a covalent bond with the ligand which prolongs the

lifetime of the complex. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by modifying the anti-chelate antibody and chelate, e.g., DOTA, used in the method taught by Hansen et al. in view of the teachings of Chmura et al., one would achieve a method of prolonging the lifetime of the complex at the target site in vivo.

Therefore, No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brandon J Fetterolf, PhD
Patent Examiner
Art Unit 1642

BF